

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 12 and 13 have been cancelled without prejudice and replaced with new claims 19-22. The new claims have been presented to be consistent with claims 16 and 17 submitted with our Amendment of November 22, 2003. Also, claims 16-18 have been amended to effect minor corrections thereto. Support the claim amendments and new claims is readily apparent from the teachings of the specification and the original claims.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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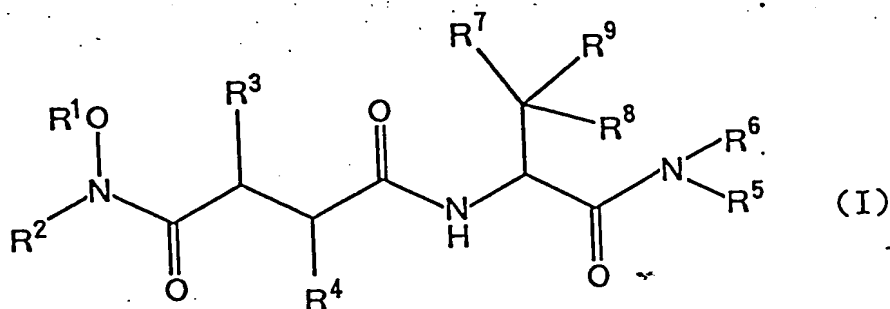
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(Amended)
16. A compound having the following formula (I):



wherein R¹, R², R⁶, R⁷ and R⁸ are each hydrogen,

1) R³ is (C₁-C₉) alkyl,

R⁴ is (C₃-C₉) alkyl,

R⁵ is (C₁-C₄) alkyl,

R⁹ is -X-Y, and Y is -A-B or -B,

wherein X, Y, A and B are selected from the following combinations:

① X is (C₁-C₆) alkylene, Y is -A-B, A is imino and B is amidino;

② X is (C₁-C₆) alkylene, Y is -B and B is amino;

③ X is phenylene, Y is -A-B, A is lower (C₁-C₄) alkylene-imino and B is lower (C₁-C₄) acylimidoyl;

④ X is (C₁-C₆) alkylene, Y is -A-B, A is imino and B is selected from the group consisting of lower (C₁-C₄) acylimidoyl and benzimidoyl;

⑤ X is phenylene, Y is -A-B, A is lower (C₁-C₄) alkyl and B is amino; and

⑥ X is phenylene, Y is -A-B, A is imino and B is selected from the group consisting of tetra-lower (C₁-C₄) alkyl bis(phosphono)methyl and tri-lower (C₁-C₄) alkyl

bis(phosphono)methyl;

2) R^3 is (C_1-C_9) alkyl,

R^4 is (C_3-C_9) alkyl,

R^5 is hydroxy-substituted (C_1-C_6) alkyl or a nitrogen-containing heterocyclic radical,

R^9 is $-X-Y$, and Y is $-A-B$,

wherein X is (C_1-C_6) alkylene,

A is imino and

B is lower (C_1-C_4) acylimidoyl;

3) R^3 is (C_1-C_9) alkyl,

R^4 is (C_3-C_9) alkyl,

① R^5 is (C_3-C_7) cycloalkyl,

R^9 is $-X-Y$, and Y is $-B$,

wherein X is (C_1-C_6) alkylene and

B is amino; or

② R^5 is a nitrogen-containing heterocyclic radical,

R^9 is $-X-Y$, and Y is $-A-B$,

wherein X is phenylene,

A is lower (C_1-C_4) alkylene-imino and

B is lower (C_1-C_4) acylimidoyl;

4) R^3 is (C_1-C_9) alkyl,

R^4 is (C_3-C_9) alkyl,

R^5 is carboxy-substituted lower (C_1-C_4) alkyl, di-lower (C_1-C_4) alkylamino-substituted lower (C_1-C_4) alkyl or hydroxy-substituted (C_1-C_6) alkyl, and

R^9 is $-X-Y$,

wherein X is phenylene and

Y is -A-B,

wherein A and B are selected from the following combinations:

- ① A is lower (C₁-C₄) alkylene-imino and
B is lower (C₁-C₄) acylimidoyl; and
- ② A is lower (C₁-C₄) alkylene and
B is amino;

5) R³ is (C₁-C₉) alkyl,

R⁴ is (C₃-C₉) alkyl,

① when R⁵ is hydroxy-substituted (C₁-C₆) alkyl,

R⁹ is -X-Y,

wherein X is phenylene and

Y is -A-B,

wherein

A is lower (C₁-C₄) alkylene-imino and

B is lower (C₁-C₄) acylimidoyl; or

② when R⁵ is lower (C₁-C₄) alkyl,

R⁹ is -X-Y,

wherein X is (C₁-C₆) alkylene and

Y is -A-B,

wherein A is imino and

B is amidino;

6) R³ is phenyl-lower (C₁-C₄) alkyl,

R⁴ is (C₃-C₉) alkyl,

① R⁵ is lower (C₁-C₄) alkyl,

R⁹ is -X-Y, and Y is -A-B,

wherein X is phenylene and

A is lower (C₁-C₄) alkylene and

B is amino; or

② R^5 is di-lower (C_1-C_4) alkylamino-substituted lower (C_1-C_4) alkyl, hydroxy-substituted (C_1-C_6) alkyl or lower (C_1-C_4) alkyl,

R^9 is -X-Y, and Y is -A-B;

wherein X is (C_1-C_6) alkylene and

A is imino and

B is lower (C_1-C_4) acylimidoyl;

7) R^3 is nitrogen-containing heterocyclic radical-substituted lower (C_1-C_4) alkyl, carboxy-substituted phenyl-lower (C_1-C_4) alkyl, amino-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, hydroxy-substituted phenyl-lower (C_1-C_4) alkyl, lower (C_1-C_4) alkoxy-carbonyl-substituted phenyl-lower (C_1-C_4) alkyl, oxygen-containing (C_1-C_8) straight chain or branched alkyl, or hydroxy-substituted (C_1-C_8) alkyl; ✓

R^4 is (C_3-C_9) alkyl,

R^5 is lower (C_1-C_4) alkyl,

R^9 is -X-Y, and Y is -B,

wherein X is ~~trimethylene~~ and
(C_1-C_6) alkylene ✓

B is amino;

8) ① R^3 is (C_1-C_9) alkyl, and

R^4 is hydroxy-substituted (C_3-C_8) alkyl, or

② R^3 is nitrogen-containing heterocyclic radical-substituted lower (C_1-C_4) alkyl, and

R^4 is (C_3-C_9) alkyl,

R^5 is lower (C_1-C_4) alkyl,

R^9 is -X-Y, and Y is -B,

wherein X is (C_1-C_6) alkylene and

B is amino;

9) R^3 is amino-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, lower (C_1-C_4) acylimido-ylimino-substituted (C_1-C_6) alkyl, lower (C_1-C_4) alkylimino-substituted (C_1-C_6) alkyl, nitrogen-containing heterocyclic radical-substituted lower (C_1-C_4) alkylimino-substituted (C_1-C_6) alkyl, or isopropyliminomethylbenzyl,

R^4 is (C_3-C_9) alkyl,

R^5 is lower (C_1-C_4) alkyl,

R^9 is hydrogen;

10) R^3 is aryloxy-substituted lower (C_1-C_4) alkyl, (C_3-C_7) cycloalkyl-substituted lower (C_1-C_4) alkyl, arylsulfonamido-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, alkylsulfonamido-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, or amino-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl,

R^4 is (C_3-C_9) alkyl,

R^5 is lower (C_1-C_4) alkyl,

R^9 is -X-Y, and Y is -A-B,

wherein X is (C_1-C_6) alkylene,

A is imino and

B is amidino;

11) R^3 is phenyl-lower (C_1-C_4) alkyl,

R^5 is lower (C_1-C_4) alkyl,

(i) when R^4 is (C_3-C_9) alkyl,

R^9 is -X-Y, and Y is -A-B,

wherein X is (C₁-C₆) alkylene,

A is imino and

unsubstituted or optionally
substituted

B is amidino;

② when R⁴ is aryl-lower (C₁-C₄) alkyl,

R⁹ is -X-Y, and Y is -A-B,

wherein X is (C₁-C₆) alkylene,

A is imino and

B is amidino; or

③ when R⁴ is (C₃-C₉) alkyl,

R⁹ is -X-Y, and Y is -B,

wherein X is (C₁-C₆) alkylene, and

B is amino;

12) R³ is amino-substituted lower (C₁-C₄) alkyl-substituted
phenyl-lower (C₁-C₄) alkyl,

R⁴ is (C₃-C₉) alkyl,

R⁵ is lower (C₁-C₄) alkyl,

R⁹ is -X-Y, and Y is -B,

wherein X is (C₁-C₆) alkylene, and

B is amino;

13) R³ is amino-substituted phenyl-lower (C₁-C₄) alkyl,

R⁴ is (C₃-C₉) alkyl,

R⁵ is di-lower (C₁-C₄) alkylamino-substituted lower
(C₁-C₄) alkyl,

R⁹ is -X-Y, and Y is -A-B,

wherein X is (C₁-C₆) alkylene, and

A is imino and

B is lower (C₁-C₄) acylimidoyl;

guanidino
14) R^3 is ~~guanido~~-substituted phenyl-lower (C_1-C_4) alkyl,
~~guanido~~-substituted lower (C_1-C_4) alkyl-substituted
phenyl-lower (C_1-C_4) alkyl, or amino-substituted lower
(C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl,
 R^4 is (C_3-C_9) alkyl,
 R^5 is lower (C_1-C_4) alkyl,
 R^9 is -X-Y, and Y is -B,
wherein X is (C_1-C_6) alkylene, and
B is amino; or

15) R^3 is amino-substituted lower (C_1-C_4) alkyl-substituted
phenyl-lower (C_1-C_4) alkyl,
 R^4 is (C_3-C_9) alkyl,
 R^5 is lower (C_1-C_4) alkyl,
 R^9 is -X-Y, and Y is -A-B,
wherein X is phenylene,
A is lower (C_1-C_4) alkylene, and
B is amino;

or a pharmaceutically acceptable salt or solvate thereof.

(Amended)

17.↓ The compound according to claim 16 wherein

R^1 , R^2 , R^6 , R^7 and R^8 are each hydrogen,

1) R^3 is methyl,

R^4 is isobutyl,

R^5 is methyl,

R^9 is -X-Y and Y is -A-B or -B

wherein X, Y, A and B are selected from the following

combinations:

- ① X is methylene or ethylene, Y is -A-B, A is imino and B is amidino;
- ② X is ethylene or trimethylene, Y is -B and B is amino;
- ③ X is phenylene, Y is -A-B, A is methyleneimino and B is acetimidoyl;
- ④ X is trimethylene, Y is -A-B, A is imino and B is selected from the group consisting of acetimidoyl, propionimidoyl and benzimidoyl;
- ⑤ X is phenylene, Y is -A-B, A is methylene and B is amino; and
- ⑥ X is phenylene, Y is -A-B, A is imino and B is selected from the group consisting of tetra-ethyl bis(phosphono)methyl, tetra-methyl bis(phosphono)methyl, tri-ethyl bis(phosphono)methyl and tri-methyl bis(phosphono)methyl;

2) R^3 is methyl,

R^4 is isobutyl,

R^5 is 2-hydroxy-1-methylethyl or piperidyl,

R^9 is -X-Y, and Y is -A-B,

wherein X is trimethylene,

A is imino and

B is acetimidoyl;

- 3) R^3 is methyl,
 R^4 is isobutyl,
 ① R^5 is cyclopropyl,
 R^9 is -X-Y, and Y is -B,
 wherein X is ethylene and
 B is amino;
- ② R^5 is morpholino,
 R^9 is -X-Y, and Y is -A-B,
 wherein X is phenylene,
 A is methyleneimino and
 B is acetimidoyl;
- 4) R^3 and R^4 are each isobutyl,
 R^5 is 2-carboxyethyl, 2-dimethylaminoethyl or
 2-hydroxyethyl,
 R^9 is -X-Y,
 wherein X is phenylene and
 Y is -A-B,
 wherein A and B are selected from the following
 combinations:
 ① A is methyleneimino and
 B is acetimidoyl; and
 ② A is methylene and
 B is amino;
- 5) R^3 and R^4 are each isobutyl,
 ① when R^5 is 2-hydroxy-1,1-dimethylethyl,
 R^9 is -X-Y,
 wherein X is phenylene and
 Y is -A-B,
 wherein A is methyleneimino and
 B is acetimidoyl;

- ② when R^5 is methyl,
 R^9 is $-X-Y$,
 wherein X is methylene or ethylene and
 Y is $-A-B$,
 wherein A is imino and
 B is amidino;

6) R^3 is phenylpropyl,
 R^4 is isobutyl,

- ① R^5 is methyl,
 R^9 is $-X-Y$, and Y is $-A-B$,
 wherein X is phenylene and
 A is methylene and
 B is amino; or

- ② R^5 is 2-dimethylaminoethyl, 2-hydroxyethyl or methyl,
 R^9 is $-X-Y$, and Y is $-A-B$,
 wherein X is trimethylene,
 A is imino and
 B is acetimidoyl;

7) R^3 is morpholinopropyl, carboxyphenylpropyl,
 aminomethylphenylpropyl, hydroxyphenylpropyl,
 methoxycarbonylphenylpropyl, piperidinypropyl,
 iso-butyloxyethyl, butoxyethyl, ethoxyethoxyethyl or
 hydroxyoctyl,

R^4 is isobutyl,

R^5 is methyl,

R^9 is $-X-Y$, and Y is $-B$,

wherein X is trimethylene and
 B is amino;

- 8) ① R^3 is isobutyl, and
 R^4 is hydroxyoctyl, or
② R^3 is (3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-
propyl, and
 R^4 is isopropyl,
 R^5 is methyl,
 R^9 is -X-Y, and Y is -B,
wherein X is trimethylene and
B is amino;

- 9) R^3 is aminomethylphenylpropyl, aminomethylbenzyl,
acetimidoyliminopentyl, isopropyliminopentyl,
(pyridin-4-ylmethylimino)pentyl or
isopropyliminomethylbenzyl,
 R^4 is isobutyl,
 R^5 is methyl, and
 R^9 is hydrogen;

- 10) R^3 is phenoxyethyl, cyclohexylpropyl, toluenesulfonamido-
methylbenzyl, methanesulfonamidomethylbenzyl or
phthalimidomethylbenzyl,
 R^4 is isobutyl,
 R^5 is methyl, and
 R^9 is -X-Y, and Y is -A-B,
wherein X is ethylene,
A is imino and
B is amidino;

- 11) R^3 is phenylpropyl,
 R^5 is methyl,
① when R^4 is isobutyl,
 R^9 is -X-Y, and Y is -A-B,
wherein X is methylene,
A is imino and
B is amidino;

② when R^4 is naphthylmethyl,
 R^9 is $-X-Y$, and Y is $-A-B$,
wherein X is ethylene,
 A is imino and
 B is amidino; or

③ when R^4 is isopropyl,
 R^9 is $-X-Y$, and Y is $-B$,
wherein X is trimethylene, and
 B is amino;

12) R^3 is aminomethylphenylpropyl,

① R^4 is isobutyl,
 R^5 is methyl,
 R^9 is $-X-Y$, and Y is $-B$,
wherein X is methylene or ethylene, and
 B is amino;

② R^4 is isopropyl,
 R^5 is methyl,
 R^9 is $-X-Y$, and Y is $-B$,
wherein X is ethylene, and
 B is amino;

13) R^3 is aminophenylpropyl,

R^4 is isobutyl,
 R^5 is dimethylaminoethyl,
 R^9 is $-X-Y$, and Y is $-A-B$,
wherein X is trimethylene, and
 A is imino and
 B is acetimidoyl;

14) R^3 is guanidinophenylpropyl, ~~guanido~~aminomethylphenylpropyl or
aminomethylbenzyl, ~~guanidino~~

R^4 is isobutyl,

R^5 is methyl, and

R^9 is -X-Y, and Y is -B,

wherein X is ethylene, and

B is amino; or

15) R^3 is aminomethylbenzyl,

R^4 is isobutyl,

R^5 is methyl, and

R^9 is -X-Y, and Y is -A-B,

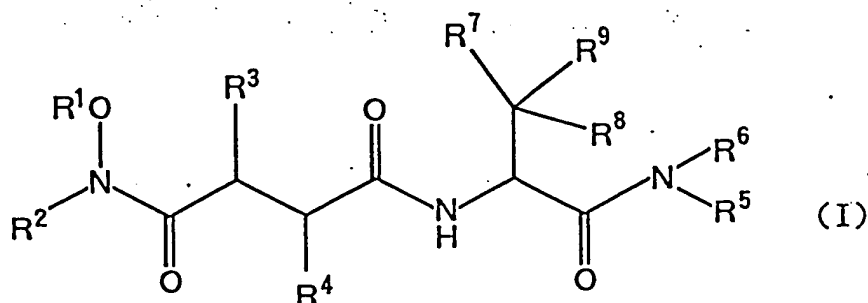
wherein X is phenylene,

A is methylene, and

B is amino.

(Amended)

18.↓ A compound having the following formula (I):



wherein R¹, R², R⁶, R⁷ and R⁸ are each hydrogen,

1) R³ is methyl,

R⁴ is isobutyl,

R⁵ is methyl,

R⁹ is -X-Y, and Y is -A-B or -B,

wherein X, Y, A and B are selected from the following combinations:

① X is (C₁-C₆) alkylene, Y is -A-B, A is imino and B is amidino;

② X is (C₁-C₆) alkylene, Y is -B and B is amino;

③ X is phenylene, Y is -A-B, A is methyleneimino and B is acetimidoyl;

④ X is trimethylene, Y is -A-B, A is imino and B is selected from the group consisting of lower (C₁-C₄) acylimidoyl and benzimidoyl;

⑤ X is phenylene, Y is -A-B, A is methylene and B is amino; and

⑥ X is phenylene, Y is -A-B, A is imino and B is selected from the group consisting of tetra-lower (C₁-C₄) alkyl bis(phosphono)methyl and tri-lower (C₁-C₄) alkyl bis(phosphono)methyl;

- 2) R^3 is methyl,
 R^4 is isobutyl,
 R^5 is 2-hydroxy-1-methylethyl or piperidyl,
 R^9 is -X-Y, and Y is -A-B,
 wherein X is trimethylene,
 A is imino and
 B is acetimidoyl;
- 3) R^3 is methyl,
 R^4 is isobutyl,
 ① R^5 is cyclopropyl,
 R^9 is -X-Y, and Y is -B,
 wherein X is ethylene and
 B is amino;
 ② R^5 is morpholino,
 R^9 is -X-Y, and Y is -A-B,
 wherein X is phenylene,
 A is methyleneimino and
 B is acetimidoyl;
- 4) R^3 and R^4 are each isobutyl,
 R^5 is 2-carboxyethyl, 2-dimethylaminoethyl or
 2-hydroxyethyl,
 R^9 is -X-Y,
 wherein X is phenylene and
 Y is -A-B,
 wherein A and B are selected from the following
 combinations:
 ① A is methyleneimino and
 B is acetimidoyl; and
 ② A is methylene and
 B is amino;

- 5) R^3 and R^4 are each isobutyl,
 ① when R^5 is 2-hydroxy-1,1-dimethylethyl,
 R^9 is -X-Y,
 wherein X is phenylene and
 Y is -A-B,
 wherein A is methyleneimino and
 B is acetimidoyl;
- ② when R^5 is methyl,
 R^9 is -X-Y,
 wherein X is (C_1-C_6) alkylene and
 Y is -A-B,
 wherein A is imino and
 B is amidino;
- 6) R^3 is phenylpropyl,
 R^4 is isobutyl,
 ① R^5 is methyl,
 R^9 is -X-Y, and Y is -A-B,
 wherein X is phenylene and
 A is methylene and
 B is amino; or
- ② R^5 is 2-dimethylaminoethyl, 2-hydroxyethyl or methyl,
 R^9 is -X-Y, and Y is -A-B,
 wherein X is trimethylene,
 A is imino and
 B is acetimidoyl;
- 7) R^3 is nitrogen-containing heterocyclic radical-substituted
 propyl, carboxyphenylpropyl, aminomethylphenylpropyl,
 hydroxyphenylpropyl, methoxycarbonylphenylpropyl,
 oxygen-containing (C_1-C_8) straight chain or branched
 alkyl or hydroxyoctyl, R^4
 R^4 is isobutyl,
 R^5 is methyl,
 R^9 is -X-Y, and Y is -B,

wherein X is trimethylene and
B is amino;

- 8) ① R^3 is isobutyl, and
 R^4 is hydroxyoctyl, or
② R^3 is (3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-
propyl, and
 R^4 is isopropyl,
 R^5 is methyl,
 R^9 is -X-Y, and Y is -B,
wherein X is trimethylene and
B is amino;

- 9) R^3 is amino-substituted methyl-substituted phenyl-lower
(C_1-C_4) alkyl, acetimidoyliminopentyl,
isopropyliminopentyl, (pyridin-4-ylmethylimino)pentyl
or isopropyliminomethylbenzyl,
 R^4 is isobutyl,
 R^5 is methyl, and
 R^9 is hydrogen;

- 10) R^3 is phenoxyethyl, cyclohexylpropyl, toluenesulfonamido-
methylbenzyl, methanesulfonamidomethylbenzyl or
phthalimidomethylbenzyl,
 R^4 is isobutyl,
 R^5 is methyl, and
 R^9 is -X-Y, and Y is -A-B,
wherein X is ethylene,
A is imino and
B is amidino;

11) R^3 is phenylpropyl,

R^5 is methyl,

① when R^4 is isobutyl,

R^9 is -X-Y, and Y is -A-B,
wherein X is methylene,

A is imino and

B is amidino;

② when R^4 is naphthylmethyl,

R^9 is -X-Y, and Y is -A-B,
wherein X is ethylene,

A is imino and

B is amidino; or

③ when R^4 is isopropyl,

R^9 is -X-Y, and Y is -B,

wherein X is trimethylene, and

B is amino;

12) R^3 is aminomethylphenylpropyl,

R^4 is (C_3-C_9) alkyl,

R^5 is methyl,

R^9 is -X-Y, and Y is -B,

wherein X is (C_1-C_6) alkylene, and

B is amino;

13) R^3 is aminophenylpropyl,

R^4 is isobutyl,

R^5 is dimethylaminoethyl,

R^9 is -X-Y, and Y is -A-B,

wherein X is trimethylene, and

A is imino and

B is acetimidoyl;

14) R^3 is guanidinophenylpropyl, ~~guanidomethylphenylpropyl~~ ^{guanidino}
or aminomethylbenzyl, ✓

R^4 is isobutyl,

R^5 is methyl, and

R^9 is -X-Y, and Y is -B,

wherein X is ethylene, and

B is amino; or

15) R^3 is aminomethylbenzyl,

R^4 is isobutyl,

R^5 is methyl, and

R^9 is -X-Y, and Y is -A-B,

wherein X is phenylene,

A is methylene, and

B is amino;

or a pharmaceutically acceptable salt or solvate thereof.